REMARKS

Claims 1-29 are pending in the application. Claims 1, 8, 9, and 10 have been amended to better clarify what Applicants regard as the invention. Claims 5, 6, 12, 22 and 24, which were objected to as depending from rejected claims, but as noted by the Examiner would be allowable if rewritten in independent form including all of the limitations of the base claims and any intervening claims, have been amended as suggested by the Examiner. No new matter has been added by way of this amendment. Thus, as a result of the foregoing amendment, claims 1-29 remain under consideration.

The Examiner has noted that if Applicants desire priority under 35 U.S.C. 119(e) based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application and should appear as the first sentence following the title. Applicants have amended the specification accordingly and respectfully request entry of the paragraph claiming priority to the earlier filed provisional into the application as filed.

Claims 5, 6, 12, 22 and 24 were objected to as being dependent upon a rejected base claim. Applicants have amended the claims as suggested by the Examiner and have rewritten the claims in independent form and have incorporated the limitation of the base claim and the intervening claims. Withdrawal of this objection is respectfully requested.

Claims 1-4, 11, 13-17 and 19-21 were rejected under 35 U.S.C 102(b) as being anticipated by Zheng et al. Furthermore, claims 1-3, 7-11, 13-21 and 23 were rejected under 35 U.S.C. 102(b) as being anticipated by Sabatini et al. Applicants respectfully traverse the Examiner's rejection, and have amended the base claim to better clarify what Applicants believe to be the invention. Support for the amendment can be found on page 3, paragraph 8. Applicants have also provided evidence as to the differences between the cited references and the instant application. Applicants believe that the amendments and arguments provided to Examiner obviate this rejection. Thus, Applicants respectfully request withdrawal of this rejection.

Claims 8-10 and 25-29 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Applicants respectfully traverse the Examiner's rejection and have also amended the claims to better clarify the invention. Support for the amendments can be

found on page 4, paragraph 12; on page 5, paragraph 17; on page 10, paragraph 44; on page 15, paragraph 64; page 18, paragraph 71; page 27, paragraph 99 and further on page 30, paragraph 105. Thus, Applicants respectfully request withdrawal of the rejection.

Claim for Priority

In response to the Examiner's assertion that the specification does not include the particulars related to priority to the earlier filed provisional application, the specification has been amended to include reference to provisional application, U.S. 60/ 268,626, filed on February 14, 2001. Applicants respectfully request entry of this paragraph into the specification before current paragraph [0001] and request renumbering of the paragraphs that follow.

Claim Objections

Claim numbers 5, 6, 12, 22 and 24 are objected to because they are dependent from rejected claims. Applicants have rewritten the claims in independent form as suggested by the Examiner and have incorporated the limitation of the base claim and the intervening claims. Accordingly, withdrawal of this objection is respectfully requested.

Claim Rejections under 35 U.S.C. §102

Claims 1-4, 11, 13-17 and 19-21 were rejected under 35 U.S.C 102(b) as being anticipated by Zheng et al. Furthermore, claims 1-3, 7-11, 13-21 and 23 were rejected under 35 U.S.C. 102(b) as being anticipated by Sabatini et al. Applicants respectfully traverse the Examiner's rejection, and have amended the base claim to better clarify what Applicants believe to be the invention, and to further differentiate the current invention over the cited references. Support for the amendment can be found on page 3, paragraph 8.

Applicants assert that there are discrete differences between the teachings of Zheng et al. and the present application. For example, Zheng et al. utilize reagents such as PCBZL and mix these reagents with biodegradable polymers such as poly(D,L-lactic-co-glycolic acid) or poly(L-lactic acid) and forms films which are used to coat wells of a tissue culture plate. These surfaces are subsequently modified with PEI, and DNA is then

attached to the PEI. These culture wells are then used for plating cells for transfection of the DNA.

Applicants note that the difference between the present invention and the Zheng reference is the fact that the present invention calls for the formation of the nucleic acid-polylinker complex **prior to** attachment to the solid substrate. The Examiner's attention is drawn to page 3, paragraph 8 of the instant application, wherein it states:

> *"**The nucleic acid-polylinker complexes are immobilized to the surface of a support substrate by a functional group attached to the polylinker.** A polylinker modified by a functional group may attach to the support substrate directly or may attach through a modifying functional group present on the support substrate. **The polylinker may be modified with a functional group before or after formation of the complex, but the complex must be formed prior to attachment to the solid support."***

With respect to Sabatini et al., the Examiner has noted that Sabatini et al. teach a method of transfecting cells comprising combining DNA with a lipid transfection agent, followed by spotting the mixture on a glass slide where it is **allowed to dry**, followed by contact with the cells which permits transfection to occur. Furthermore, applicants respectively point out that the depositing of the nucleic acid molecules onto the solid surface is done **in the presence of gelatin** (see claim 1, step (a).

Accordingly, Applicants assert that the teachings of Sabatini et al differ from the current application in several aspects.

In one aspect, Sabatini et al. teach that the DNA is affixed to the solid surface by way of **drying in the presence of a protein carrier, e.g. gelatin**. This allows for deposition of the DNA in discrete locations on the slide.

In a second aspect, Sabatini et al. do not teach the formation of a nucleic acid-polylinker complex as Applicants have described in the instant application, whereby the **nucleic acid-polylinker complex is formed prior to attachment to the solid support**.

In a third aspect, Sabatini et al. teach a requirement for allowing the DNA to dry on the slide prior to addition of the cells to be transfected. Applicants' invention does does not contain this limitation. Since there is no apparent means to chemically couple

the DNA to the support matrix in the Sabatini et al. reference, as Applicants utilize in the present application, it would appear that the only means for the discrete placement of the DNA to the surface of the support is by a drying means.

In a fourth aspect, Sabatini et al. do not provide for the "specificity" of the interaction of the nucleic acid attached to the solid support, such as that described in the present application, which allows for more defined spatial arrangement of the nucleic acid-polylinker complexes. As noted in Applicants' invention, the DNA/PLL complexes are incubated on surfaces to specifically tether the complexes through the biotin and avidin, streptavidin or neutravidin interaction.

Accordingly, neither Zheng et al., nor Sabatini et al. teach or suggest the methods of the present invention in the claims as currently amended. Based on the foregoing, withdrawal of the rejection is respectfully requested.

Claim Rejections under 35 U.S.C. §112

Claims 8-10 and 25-29 have been rejected under 35 U.S.C. 112, second paragraph as being indefinite.

Applicants respectfully traverse Examiner's rejection and have amended the claims to better clarify what Applicants believe to be the invention.

In particular, the Examiner has asserted that the term "modified polylinker" and "non-modified polylinker" is not clear in that one of skill in the art cannot look at a structure and know if it has been "modified" from some other compound. Applicants respectfully traverse the rejection for the following reasons.

The Examiner's attention is drawn to the various pages and paragraphs cited above, whereby it would be obvious to one skilled in the art that the term "modified" or "non-modified", as noted in the present invention, are chemical modifications that are commonly used by a skilled artisan to add functional moieties onto proteins or nucleic acids to allow for a chemical interaction and bonding to occur. For example, on page 4, paragraph 12:

> *"The support substrate either contains or can be chemically modified to contain a functional group that allows the support substrate to covalently bind to a bifunctional crosslinker or polylinker modified to have a functional group."*

Further clarification of the chemistry involved in the modifications is shown on page 5, paragraph 17:

> *"In another embodiment,* ***the polylinkers are modified with a first functional group*** *prior to step (a) and* ***the support substrate is modified with a second functional group capable of interacting with the first functional group.*** *In one embodiment, the nucleic acid is contacted with both modified and unmodified polylinkers, forming nucleic acid-polylinker complexes which bind to the support substrate with varying binding strengths, and thus are released over a period of time as a result of the different bond strengths. In another embodiment, the bond between the polylinker and the support substrate is reversible. In a further embodiment, the support substrate may be modified with a second functional group able to interact with the first functional group modifying a polylinker.* ***In a specific embodiment, polylinker is poly-L-lysine (PLL), the first functional group is biotin, and the second functional group is avidin, strepavidin, or an avidin derivative."***

Furthermore, on page 18, paragraph 71:

> *"All cationic polymers contain high densities of primary amines, which are protonatable at neutral pH. This high density of positive charges allows the cationic polymers to form stable complexes with non-viral DNA. The cationic polymers self-assemble with DNA to generate condensed structures (40 – 100 nm in diameter) capable of entering the cell. Cationic polymers include polyallylamine, peptoids, methacrylamide, and cyclodextrin containing polymers. Such polymers vary widely in their structure, which ranges from linear to highly branched molecules and influences their complexation with nucleic acids and their transfection efficiency. In addition to providing positive charges for DNA complexation, the primary amines also serve as functional groups with which to* ***chemically modify*** *the polymers with ligands and peptides that can enhance one or more of the steps in the transfection process."*

The Examiner's attention is also drawn to page 27, paragraph 99:

> "*Example 2 describes the synthesis of biotinylated PLL and complexation with DNA. Polylysine was covalently modified with biotin residues either through an N-terminal cysteine side chain (K_{19}) or through an amine (K_{150}). HPLC analysis of the initial peptide (K_{19}) and the peptide reaction mixture (K_{19}-B) demonstrated that the reaction proceeded to completion (Fig. 7), as evidenced by the increase in molecular weight in the reaction mixture and the absence of the lower molecular weight K_{19} peak. Mass spectrometry (Fig. 8) suggests that the approach for modifying the peptide K_{19} results in the attachment of a single biotin group. A good correspondence was found between the theoretically expected molecular weight for K_{19} modified with a single biotin (3158 Da), and the experimentally obtained molecular weight (3157.66 ± 0.77 Da). Alternatively,* ***the chemistry employed for modification*** *of K_{150} allows for multiple biotin residues to be attached per PLL. The K_{150}-B synthesis resulted in a 3.1:1 molar ratio of biotin to K_{150} by using a 10:1 molar ratio of biotinylation reagent to K_{150} in the reaction mixture.*"

And finally, on page 30, paragraph 105:

> "*Experiment 1. Plasmid DNA encoding either green fluorescent protein (GFP) or luciferase was complexed with modified poly-L-lysine (PLL) at a ratio of 3.1. PLL was modified by PLL reaction with the bifunctional cross-linker sulfosuccinimidyl 6-[3'-(2-pyridyldithio) -propionamido] hexanoate (Sulfo-LC-SPDP, Pierce) prior to DNA complexation at a 1:1 molar ratio. The PLL/DNA complexes were subsequently incubated with glass slides that were modified with (3-mercaptopropyl) -trimethoxysilane (MPTS, Sigma) to create pendant thiol groups. Following coupling of PLL/DNA complexes to the slide, the surfaces were extensively washed and treated with trypsin to degrade the PLL and release the DNA into solution. The surface density of DNA was determined to be 3.9 ± 0.78 $\mu g/cm^2$. Control slides incubated with PLL/DNA complexes without the sulfo-LC-SPDP tether had a surface density of 0.3 ± 0.1 $\mu g/cm^2$ (Fig. 3).*"

It is obvious from the foregoing that the modifications referred to in the present invention are chemical modifications that aid in the reactivity and bonding or attachment of one moiety to another. As such, the claims have been amended to recite the term "chemical modification" to note that the attachment of a functional group by chemical means allows for subsequent attachment to other groups or substrates. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 25-29 have also been rejected under 35 U.S.C. 112, second paragraph as being indefinite. In particular, the Examiner has asserted that the term "specifically bound" is a matter of binding affinity, and thus a matter of degree, which is not specified or defined in the instant specification or the prior art, and as such, the metes and bounds of the claims are not defined.

Applicants respectfully traverse the Examiner's rejection for the following reasons. The Examiner's attention is drawn to the Example section on pages 30-35, wherein the preparation of the DNA with a polylinker (PLL) and the subsequent attachment to the substrate is described. Applicants respectfully point out that in the examples shown, the first functional group that is coupled to the polylinker PLL is biotin and the second functional group attached to the substrate is one of the following: avidin, streptavidin or neutravidin. The affinity and specificity of biotin for avidin, streptavidin and neutravidin is well known to the skilled artisan. Accordingly, Applicants assert that while a specific definition has not been provided in the specification for the term "specifically bound", the meaning of this term would be obvious to the skilled artisan upon reading the instant application.

One of the embodiments of the present invention is to spatially control the delivery of the nucleic acid to the substrate and then to the cell, which is subsequently exposed to the nucleic acid. The Examiner's attention is drawn to page 23, paragraph 88, whereby it states:

> *"...In a particular embodiment the condensed nucleic acid of the solid substrate had been delivered in a spatially controlled pattern to the solid substrate...."*

As related to this, it also states on page 33, paragraph 114 that:

*"DNA/PLL complexes were incubated on surfaces to **specifically tether the complexes through the biotin-neutravidin binding."***

Accordingly, Applicants assert that upon reading the present application, while the term "specifically bound" is not defined, there is sufficient support by way of examples to support the meaning of the term and to define the metes and bounds of the claims of the invention. Withdrawal of the rejection is respectfully requested.

Fees

A check in the amount of $55 is included for a one month extension of time. No other fees are believed to be due for the present response. However, should this be in error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or to credit any overpayments.

Conclusion

Applicants believe that the foregoing amendments to the claims place the application in condition for allowance. Withdrawal of the rejections and objections is respectfully requested. If a discussion with the undersigned will be of assistance in resolving any remaining issues, the Examiner is invited to telephone the undersigned at (201) 487-5800, ext. 118, to effect a resolution.

Respectfully submitted,

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